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DISODIUM CROMOGLYCATE, A MAST-CELL STABILIZER, ALTERS POSTRADIATION REGIONAL CEREBRAL BLOOD FLOW IN PRIMATES

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Early transient incapacitation (ETI) is the complete cessation of performance during the first 30 min after radiation exposure, and performance decrement (PD) is a reduction in performance at the same time. Supralethal doses of radiation have been shown to produce a marked decrease in regional cerebral blood flow in primates concurrent with systemic hypotension and a dramatic release of mast-cell histamine. In an attempt to elucidate mechanisms underlying the radiation-induced ETI/PD phenomena and the postradiation decrease in cerebral blood flow, primates were given the mast-cell stabilizers disodium cromoglycate (DSCG) or BRL 22321 (Beecham Pharmaceuticals, Research Division) before exposure to 100 Gy whole-body gamma radiation. Hypothalamic and cortical blood flows were measured by hydrogen clearance, before and after radiation exposure. Systemic blood pressures were determined simultaneously. The data indicated that DSCG was successful in diminishing postradiation decrease in cerebral blood flow. Irradiated animals pretreated with DSCG, showed only a 10% decrease in hypothalamic blood flow 60 min postradiation, while untreated, irradiated animals showed a 57% decrease. The cortical blood flow of DSCG treated, irradiated animals showed a triphasic response, with a decrease of 38% at 10 min postradiation, then a rise to 1% below baseline at 20 min, followed by a fall to 42% below baseline by 50 min postradiation. In contrast, the untreated, irradiated animals showed a steady decrease in cortical blood flow to 79% below baseline by 50 min postradiation. There was no significant difference in blood-pressure response between the treated and untreated, irradiated animals. Systemic blood pressure showed a 60% decrease at 10 min postradiation, falling to a 71% decrease by 60 min. The effects of BRL 22321 in altering postradiation blood flow in the cerebral cortex and hypothalamus were intermediate between the irradiated controls and those pretreated with DSCG, but were not considered to be significant at the concentration employed. The overall results of this study indicate that the postradiation decrease in regional cerebral blood flow may be partially alleviated by treatment with a mast-cell stabilizer.

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INTRODUCTION

Early transient incapacitation (ETI) is the complete cessation of motor performance, occuring transiently and within the first 30 min

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following exposure to supralethal doses of ionizing radiation (Kimeldorf and Hunt, 1965), and performance decrement (PD) is a reduction in performance at the same time. Since supralethal exposure to ionizing radiation such as gamma photons results in postradiation hypotension (Cockerham et al., 1984a) with the arterial blood pressure often decreasing to less than 50% of normal (Doyle et al., 1974), this is a possible explanation for ETI. In one investigation (Bruner et al., 1975) the PD was closely correlated with postradiation hypotension, the decrement following usually within a few minutes of the initial fall in blood pressure.

Postradiation hypotension produces a decrease in cerebral blood flow (CBF) even though the central nervous system (CNS) can otherwise maintain CBF under conditions of severe hypotension through the mechanism of autoregulation. One study (Chapman and Young 1968) demonstrated a dramatic fall of CBF immediately following a single 25-Gy ^{60}Co exposure, and another study (Cockerham et al., 1984c) reported a precipitous drop in regional blood flow in the visual cortex of primates exposed to 100 Gy ^{60}Co radiation. It is, therefore, conceivable that the ETI/PD phenomena following postradiation systemic hypotension may result substantially from a secondarily decreased cerebral blood flow.

There are reported elevations of circulating blood histamines in humans undergoing radiation therapy (Lasser and Stenstrom, 1954). Decreases in tissue histamine levels in rats (Eisen and Wilson, 1957), as well as increases in canine plasma histamine levels (Cockerham et al., 1984b, 1985) and primate plasma histamine levels (Alter et al., 1983; Cockerham et al., 1986; Doyle and Strike, 1977), following radiation exposure have also been reported. Histamine, stored in mast cells throughout the body (Metcalfe et al., 1981), is released under the stimulus of ionizing radiation and is implicated in radiation-induced hypotension. One study (Doyle et al., 1974) even reported the prevention or modification of radiation-induced performance changes and hypotension by the preradiation administration of an antihistamine. This study was designed to determine if the radiation-induced systemic hypotension and decreased cerebral blood flow could be mitigated by the preradiation administration of either disodium cromoglycate (DSCG) (Fisons Corporation, Bedford, Mass.) or BRL 22321 (Beecham Pharmaceuticals, Research Division), two mast-cell stabilizers (Spicer et al., 1983).

Two contrasting regions of the brain were selected for this study. The supraoptic nucleus of the hypothalamus was selected as the first region of interest, because mast cells are particularly numerous in the hypothalamus (Edvinsson et al., 1977) and the hypothalamus contains the highest histamine concentrations in the brain (Gross, 1982; Taylor et al., 1972). In contrast, the second region of interest, the postcentral

gyrus, is an area with little histamine (Taylor et al., 1972) and few mast cells (Edvinsson et al., 1977).

MATERIALS AND METHODS

Twenty-five rhesus monkeys (*Macaca mulatta*), weighing between 2.4 and 4.6 kg (3.3 ± 0.13 SEM), were used in this study. The animals were divided randomly into three groups of six animals each and one group of seven. The animals were grouped as follows: group I, 6 sham-radiated monkeys; group II, 7 radiated monkeys; group III, 6 monkeys given the mast-cell stabilizer disodium cromoglycate (DSCG) by iv infusion (100 mg/kg) 60 min before radiation; and group IV, 6 monkeys given the mast-cell stabilizer BRL 22321 iv (0.1 mg/kg) 5 min before radiation. These dosages were selected to approximate the levels reported by Spicer et al. (1983) for maximum effectiveness in rats.

Research was conducted according to the principles enunciated in the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources, National Research Council. The monkeys were initially anesthetized in their cages with an im injection of 60 mg of ketamine hydrochloride with 0.04 mg atropine sulfate and were then moved to the surgery, where the remainder of the experiment was conducted.

Approximately 3 h before radiation or sham radiation, the animals were intubated with a cuffed endotracheal tube and ventilated using a forced-volume respirator to maintain a stable blood pH and oxygen tension. After insertion of the endotracheal tube, each animal was placed on a circulating water blanket to maintain body temperature between 36 and 38°C. A rectal probe was inserted to monitor body temperature. A femoral arterial catheter was used to withdraw blood for blood gas determinations and to measure systemic arterial blood pressure using a Statham P23 Db pressure transducer. A systemic venous catheter was used to administer the DSCG, BRL 22321, physiological saline, and maintenance doses of anesthetic (α - chloralose, as needed, for a total dose of 100 mg/kg).

The animal's head was positioned on the headholder of a stereotaxic instrument (David Kopf Instruments, Tujunga, Calif.) and the scalp was shaved and incised, allowing access to the skull. Using the stereotaxic micromanipulator, the skull was marked for insertion of four electrodes, and small burr holes were drilled through the skull at these marks. Again, using the micromanipulator, one electrode was placed in the left and one in the right supraoptic nucleus of the hypothalamus (Snider and Lee, 1961). In the same manner, one electrode was placed in the left and one in the right posterior central gyrus of the parietal cortex, 4 mm each side of the longitudinal fissure. The latter two electrodes were placed so that the tips were 2 mm below the sur-

face to insure that measurements would be taken from the cortical grey matter. The electrodes were Teflon-coated, platinum–iridium wire of 0.178 mm diameter, encased in, but insulated from, rigid stainless-steel tubing (22-gauge spinal needle) with exposed tips of approximately 2 mm. The exposed dura was covered with moistened pledgets, and the electrodes were sealed and secured to the skull with dental acrylic. A stainless-steel reference electrode was placed in neck tissue.

Regional cerebral blood flow was measured by the hydrogen clearance technique for 30 min before radiation or sham radiation and for 60 min after (Aukland et al., 1964; Young, 1980). This technique is essentially an amperometric method, which measures the current induced in a platinum electrode by the reduction of hydrogen. The current produced has a linear relationship with the concentration of hydrogen in the tissue (Hyman, 1961). Hydrogen was introduced into the blood via inhalation through the endotracheal tube at a rate of approximately 5% of the normal respiratory intake for 1–2 min for each flow measurement. Blood flow was measured by each of the four electrodes every 5–10 min. The electrodes were maintained electrically at +600 mV in respect to the reference electrode to reduce possible oxygen and ascorbate interference. This method has been successfully employed in several similar studies (Cockerham et al., 1986).

Measurement of currents from each electrode were fed through the polarographic amplifier (Triangle Research and Development Corporation, Research Triangle Park, N.C.) and then to a recorder, which produced curves depicting the clearance of hydrogen from the tissues. The clearance curves were then analyzed by a PDP 11/76 computer equipped with a VT55 terminal and a Versatex plotter (Digital Equipment Corporation, Maynard, Mass.). The first 60 s after the peak of the curves was neglected to obviate contamination by arterial recirculation (Martins et al., 1974). Data points were measured every second for 60 s. The flow was calculated between every two points, and a linear regression was performed over the 60-s period.

After 30 min of baseline recording, the animals were disconnected from the respirator and recording apparatus to facilitate radiation in a separate room. After radiation, or sham radiation for controls, the animals were reconnected to the respirator and recording apparatus at 4 min postradiation, and measurements were continued for a minimum of 60 min. At 30 and 10 min before radiation or sham radiation, and at 6, 15, 30, 45, and 60 min after radiation or sham radiation, blood samples were taken via the arterial catheter to monitor stability of blood pH and oxygen tension, and respiration was adjusted to maintain preradiation levels. Body temperature was monitored and maintained with the water blanket. Mean systemic arterial blood pressure was determined via the arterial catheter for the duration of the experiment. After termi-

nation of the measurements, the location of the electrodes was examined visually for verification of placement.

Irradiation was accomplished with a bilateral, whole-body exposure to gamma-ray photons from a cobalt-60 source located at the Armed Forces Radiobiology Research Institute (AFRRI). Exposure was limited to a mean of 1.38 min at 74 Gy/min steady state, free-in-air. Dose-rate measurements at depth were made with an ionization chamber placed in a tissue-equivalent model. The measured midline tissue dose rate was 69 Gy/min, producing a calculated total dose of 100 Gy, taking into account the rise and fall of the radiation source.

Blood pressure and blood flow data were grouped into 10-min intervals, measured in relation to midtime of radiation, and plotted at the middle of the interval. The Wilcoxon rank sum test was used to analyze statistically the blood pressure and blood flow data. A 95% level of confidence was employed to determine significance. Since all the animals were treated identically before radiation or sham radiation, and since the preradiation data for the control and test animals showed no significant differences, the preradiation data for the irradiated and sham-irradiated animals were combined.

RESULTS

As seen in Fig. 1, the mean systemic arterial blood pressure (MABP) of untreated, irradiated animals decreased to 46% of the preradiation

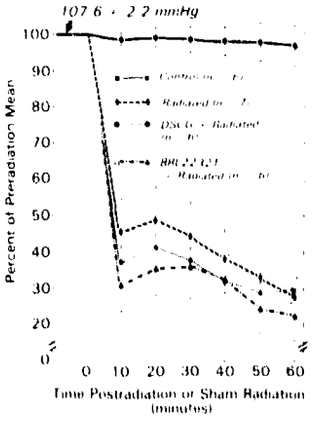

FIGURE 1. Mean (+ SEM) arterial blood pressure after exposure to 100 Gy whole-body gamma radiation, presented as percent of preradiation level. Treated groups received either 100 mg/kg DSCG at 60 min preradiation or 0.1 mg/kg BRL 22321 at 5 min preradiation.

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mean of 107.6 ± 2.2 mmHg within 10 min postradiation. A slight, non-significant rise was seen at 20 min postradiation, followed by a steady decline to a 60-min postradiation level that was 28% of the preradiation values. After sham radiation there was no significant change in MABP for the six control monkeys. The 12 treated, irradiated monkeys (groups II and III) displayed a decreased MABP that was not different statistically from the 7 untreated, irradiated monkeys. The MABP values for the irradiated groups, although not different statistically from each other, are different statistically from the sham-irradiated control group. The respiration of each subject was maintained at preradiation levels and, although not presented, the blood gas data revealed a general stability of blood pH and oxygen tension throughout the experimental period.

Figure 2 displays a preradiation mean blood flow of 64.9 ± 5.3 ml/100 g tissue • min in the supraoptic nucleus of the hypothalamus. The postradiation blood flow values for the sham-irradiated, control monkeys showed only a slight, insignificant increase during the 60 min after sham radiation. However, the postradiation values for the untreated, irradiated animals showed a rapid, significant decline to 66% of the preradiation levels at 10 min postradiation. At 60 min postradiation the blood flow had decreased to 43% of the preradiation or baseline level. There was a significant difference ($p = 0.05$) between the control

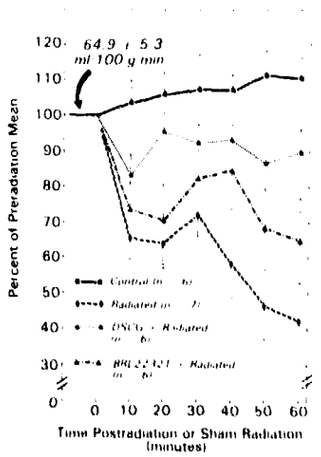

FIGURE 2. Mean (+ SEM) hypothalamic blood flow after exposure to 100 Gy whole-body gamma radiation, presented as percent of preradiation level. Treated groups received either 10 mg/kg DSCG at 60 min preradiation or 0.1 mg/kg BRL 22421 at 5 min preradiation.

and untreated, radiated groups at all postradiation times of measurement. In contrast, the hypothalamic blood flow in the DSCG-treated, irradiated monkeys fell only slightly, to about 84% by 10 min postradiation, and averaged about 90% of the preradiation baseline for the remainder of the 60 min. At the 10-min postradiation observation there was no significant difference between this group and the other two radiated groups; however, a statistically significant difference did exist between the DSCG-treated, irradiated group and the untreated, irradiated group from 20 min postradiation through the remainder of the measurements. There was no significant difference between the DSCG-treated, irradiated group and the sham-irradiated group from 20 to 60 min postradiation. Monkeys given the mast-cell stabilizer BRL 22321 (group IV) exhibited a supraoptic nucleus postradiation blood flow that decreased to 73% by 10 min postradiation and was significantly different from that of the control animals at the 10, 20, 50, and 60 min postradiation times. At no time postradiation did the BRL 22321-treated monkeys significantly differ in hypothalamic blood from the untreated, irradiated group (II) of animals or from the DSCG-treated, irradiated group (III) of animals.

The preradiation cortical blood flow, as shown in Fig. 3, was 45.0 ± 3.6 ml/100 g tissue • min. The postradiation flow for the sham-irradiated group of monkeys showed no significant changes for the 60-min observation period. The postradiation blood flow values for the untreated, radiated monkeys showed a steady decline to 21% of the preradiation levels by 50 min postradiation. These levels became significantly different ($p = 0.05$) from those of the control group at 10 min postradiation and remained that way for the remainder of the observations.

In the cortex, as in the hypothalamus, blood flow in DSCG-treated, irradiated monkeys did not follow the same pattern as in the untreated, irradiated animals. The cortical blood flow in the DSCG-treated group dropped to approximately 60% in 10 min and then increased to baseline levels at 20 min postradiation, followed by a steady decline to 58% of baseline by 50 min postradiation. The cortical blood flow values for the DSCG-treated group were significantly different ($p = 0.05$) from the control group at 10 min postradiation, but not from the untreated, irradiated group. However, at 20 and 30 min postradiation this group was significantly different from the untreated, irradiated group, but not from the control group. This relationship between the DSCG-treated group and the other two groups reversed again for the remainder of the observations, with the treated group now again significantly different from the control group, but not from the untreated, irradiated group.

The postradiation cortical blood flow for the BRL 22321-treated monkeys followed a pattern similar to the one for the DSCG-treated group, decreasing to 60% in 10 min and then increasing to 79% of the

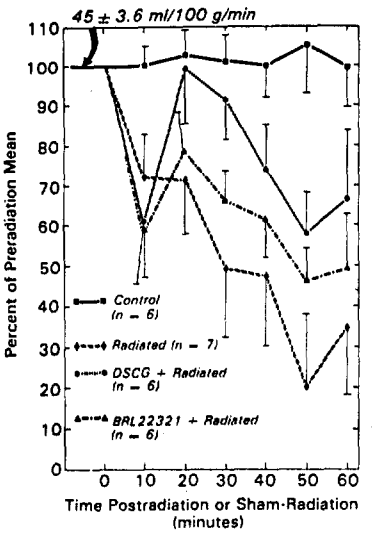

FIGURE 3. Mean (± SEM) cortical blood flow after exposure to 100 Gy whole-body gamma radiation, presented as percent of preradiation level. Treated groups received either 100 mg/kg DSCG at 60 min preradiation or 0.1 mg/kg BRL 22321 at 5 min preradiation.

preradiation level at 20 min postradiation. This increase was followed by a steady decrease to 46% of preradiation values by 50 min postradiation. At 20 min postradiation this group was not significantly different from the other three groups, but did differ from the control group at all other times. At no time postradiation did the BRL 22321-treated monkeys significantly differ from the untreated, irradiated group (II) or the DSCG-treated, irradiated group (III) in cortical blood flow.

DISCUSSION

Postradiation hypotension has been well documented in the rhesus monkey, and a critical postradiation mean arterial blood pressure (MABP) of 50–60% of the preradiation MABP must be maintained for adequate autoregulation of cerebral circulation (Chapman and Young, 1968; Doyle et al., 1974; Farrar et al., 1981). The initial precipitous decline in MABP to 46% of the preradiation levels may then be associated with the similar immediate decrease in blood flow seen in both the hypothalamus and the cerebral cortex of the untreated, irradiated animals. A similar decrease in cerebral blood flow accompanied by symptoms and signs of cerebral ischemia has been reported in

humans (Finnerty et al., 1957). On the basis of the diminished cerebral blood flow reported in these animals, one might expect a severe functional impairment of the CNS in monkeys following radiation. In fact, postradiation early transient incapacitation (ETI) has been reported in monkeys starting as early as 2 min postradiation, lasting for 10–30 min and often accompanied by severe systemic hypotension during which MABP decreased to less than 50% of normal (Bruner, 1977; Doyle et al., 1971). The decline in MABP and cerebral blood flow (CBF) reported here corresponds closely in time with the observed occurrence of ETI (Bruner, 1977; Curran et al., 1973; Doyle et al., 1974) and suggests a causal relationship between the depressed MABP, CBF, and the appearance of ETI.

However, the maintenance of a normal MABP in postradiated monkeys administered norepinephrine did not improve postradiation performance significantly above those injected with saline (Turns et al., 1971). Conversely, the antihistamine chlorpheniramine maleate was effective in reducing ETI and postradiation performance decrement, while at the same time reducing postradiation hypotension in monkeys (Doyle et al., 1974). This study, however, using the mast-cell stabilizers disodium cromoglycate (DSCG) or BRL 22321, was not able to prevent postradiation hypotension in monkeys, but was able to alter postradiation cerebral blood flow (to a significant extent in the case of DSCG).

Autoregulation of cerebral blood flow to the hypothalamus appeared to be intact in animals pretreated with DSCG, even though the postradiation MABP fell to approximately 30% of the preradiation level. Based on the high concentration of mast cells in the hypothalamus (Edvinsson et al., 1977) and the ability of DSCG to stabilize mast cells, it seems that the degranulation of mast cells may be responsible, in part, for the radiation-induced loss of autoregulation of blood flow in the hypothalamus and, therefore, partially responsible for the radiation-induced performance decrement. This contention is supported by investigators who have reported radiation-induced release of histamine from mast cells (Doyle and Strike, 1977) and the reduction of ETI by the administration of antihistamines (Doyle et al., 1974). Further, the difference in the magnitude of the protective effect of DSCG between the cortex and the hypothalamus, seen in the latter time periods, implicates a local histamine release as a mediator of the response.

The measurements of cortical blood flow in the postcentral gyrus of radiated monkeys pretreated with mast-cell stabilizers, when plotted at postradiation times (Fig. 3), present a graph strikingly similar to the performance graph of monkeys exposed to 8.9 Gy of mixed gamma–neutron radiation (Curran et al., 1973), with the same temporal relationship. This triphasic response in monkeys pretreated with mast-cell stabilizers indicates that the degranulation of mast cells is involved

with, but may not be able to completely account for, the loss of autoregulation of blood flow to the postcentral gyrus.

Even though a temporal relationship does seem to exist between cortical blood flow and ETI, the presence of other factors must not be excluded. Some other chemical factor(s) could be released by radiation, cause the release of histamine from mast cells, and produce ETI by acting as a neurotransmitter or neuromodulator in the central nervous system. Before a temporal relationship, and definitely a causal relationship, can be established, postradiation measurements of blood chemistry, cerebral blood flow, and behavioral effects must be accomplished on the same animal subject.

While the effects of BRL 22321 in altering postradiation blood flow in the cerebral cortex and hypothalamus were found to be intermediate between the irradiated controls and those pretreated with DSCG, revealing a similar trend, these results were not considered to be significant at the concentration employed. As previously mentioned, the dosages were calculated to approximate the levels reported to be maximally effective in rats (Spicer et al., 1983). Although it is difficult to compare the two studies, since different species and different perturbations were employed, the results suggest that a larger dosage of BRL 22321 may yet (as has DSCG) prove to be effective in maintaining postradiation cerebral blood flow.

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